A Meta-Analysis on the Effectivity and Efficiency of Bacterial Cellulose in Wound Healing Compared to Conventional Methods of Wound Management in Adult Patients with Venous Ulcers

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ABSTRACT

Bacterial cellulose (BC) has shown competence against plant cellulose as a structural component. Porosity and increased surface area makes BC a material of interest in wound management. Recent studies have investigated the use of BC as an alternative wound dressing to conventional wound management methods. The general objective of this study is to assess the effectiveness and efficiency of BC in wound healing compared to conventional methods in adult patients with venous ulcers (VU). The primary objective compared the reduction of mean ulcer area between experimental and conventional treatments in patients, while the secondary objectives compared pain intensity, appearance of scar formation, and wound healing tissue. Data was identified and screened through PRISMA and the ROB-2 Assessment Tool. The researchers identified four studies from which data was analyzed using DerSimonian and Laird Random Effects Model. The data revealed no significant differences between the mean ulcer area reduction before and after treatment in both groups. The BC group showed a better outcome, presenting an increase in wound healing and in patients reporting mild to no pain. BC's scar formation reported a decrease in partial skin loss prevalence rate. Despite these claims, the differences in BC and conventional treatment in terms of pain intensity, scar formation, and wound healing are not statistically significant. This concludes that BC and conventional methods are both viable for treatment of VUs in adult patients. The authors recommend that other parameters be investigated and compared, i.e. cost, production, availability of materials, allergies, and sustainability.

KEYWORDS: Bacterial cellulose; venous ulcers; Wound management

1 INTRODUCTION

Cellulose, commonly identified as a structural component in plants, also has the same properties in bacterial cell walls. This cellulose-producing bacterium in its natural habitat uses synthesized cellulose to protect itself against chemical, biological, and physical disturbances. There are several gram-negative and gram-positive bacteria that produce cellulose, however Acetobacter is described to be the primary source of microbial glucose in research studies (J. Wang et al., 2019). Bacterial cellulose (BC) is also described to be a virulence factor (Römling & Galperin, 2015). The model organism for understanding cellulose biosynthesis would be A. xylinum. Figure 1 completely describes the mechanism of synthesis from uridine diphosphoglucose (UDPGlc) to the cellulose polymer (Lustri et al., 2015; Phruksaphithak et al., 2019).

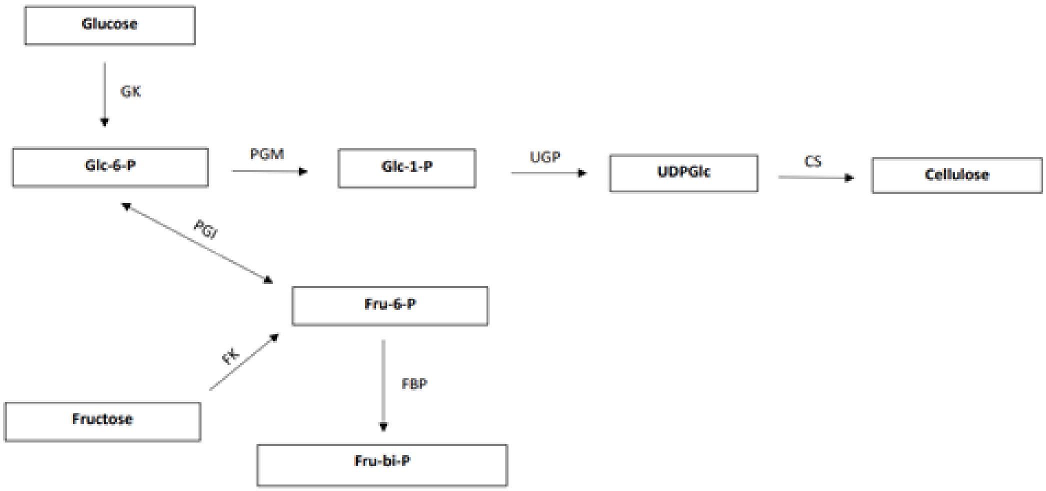

Figure 1. The biosynthesis of cellulose by A. xylinum species. (Lustri et al., 2015).

Gayarthry & Gopalaswamy (2014) compared the differences in structure of bacterial and plant cellulose and observed that the microfibrils of BC are narrow, giving rise to the material's porous structure and increased surface area. This property makes it a polymer of interest not only for engineering and industrial processes, such as edible food packaging, but also for biomedical applications in managing and treating patient wounds (Cazón & Vázquez, 2021). Innovations in wound management are not new; over the millennia, civilizations have continued to develop and discover desirable criteria for materials used in wound dressings (Shah, 2011, as cited in Dhivya et al., 2015; Daunton et al., 2012, as cited in Dhivya et al., 2015). Wound dressings are designed to contact the wound. Wounds closed with dressing are exposed to complement & growth factors, proteinases, and chemotactic, which are lost if the lesion is left open (Dhivya et al., 2015).

The attempt to close superficial areas of the skin via skin glue or sutures is known as "primary intention wound healing" (Singh et al., 2017). The wound is normally repaired with sutures or synthetic adhesive closure materials using sterile procedures to have a functional scar that heals entirely after the operation (Salcido, 2017). However, by primary intention, there is only a small window to close the wound, usually 4 to 8 hours, and the clinician's skill to approximate the wound margins is one issue, as well as contamination may cause wound closure to be delayed (Salcido, 2017).

Healing through secondary intention is the next best choice in these situations; the skin cannot be sutured right away because it must first fill connective tissue in the affected area (McCaughan et al., 2018). In addition, lesions present in this type of wound healing cannot be stitched since techniques for closure are impossible due to motility. Secondary wound healing relies on the body's natural healing processes. Frequent dressing changes and wound packing are needed in some cases. Different dressing options are available such as simple non-adherent dressings to more sophisticated options like foam, hydrocolloid, alginate, and negative pressure dressings (Dumville et al., 2014, as cited in Chetter et al., 2019).

Tertiary intention wound healing is considered the last degree and is intentionally left open to manage infection before closing the wound. The wound-closing process is delayed because microorganisms may be trapped if the wound is closed immediately (Ilankovan & Sayan, 2021). It is for infected or harmful wounds with a high bacterial content, wounds that have been infected for an extended period, or wounds with a severe crush component (Gupta et al., 2016; Salcido, 2017).

Wound dressing is considered a part of conventional wound healing and encompasses Traditional and Modern dressings (Dhivya et al., 2015). Traditional wound dressings are directly applied to cover and protect a wound by preventing the possibility of wound contamination or infection. Examples of these are gauzes, lint, plasters, bandages, and cotton wool. Modern wound dressings are also directly applied to the wound while actively preventing wound dehydration. These modern wound dressings are synthetic materials consisting of semi-permeable film, semi-permeable foam, hydrogel, hydrocolloid, and alginate (Tan et al., 2019).

Ideal wound dressings are characterized by maintaining high humidity and removing excess exudates. Additionally, they are non-toxic and non-allergenic, comfortable for patients, and cost-effective. Moreover, they can prevent the infection of microbes and allow for the exchange of oxygen. (Dart et al., 2019; Jannesari et al., 2011; Rezvani Ghomi et al., 2019; Felgueiras et al., 2020, as cited in Zheng et al., 2020).

A routinely used treatment for Chronic Venous Ulcers (CVU) is the use of substances such as essential fatty acids (EFAs) or substances containing medium-chain triglycerides (MCT), and are covered with a secondary dressing where the feet and legs are covered with gauze and bandages (Cavalcanti et al., 2017). Current treatment of CVU includes the management of secondary symptoms such as pain, edema, cramps, and limb heaviness (Bignamini & Matuška, 2020).

A similar study used a cellulose acetate mesh impregnated with EFAs called Rayon® (Silva et al., 2021). It was mentioned in the same study that collagenase dressings, sunflower oil, Unna boots, and silver sulfadiazine coverings are more commonly used in Family Health Units because of their availability and cost-effectiveness (Abbade et al., 2020; Cavalcanti et al., 2017; Colenci et al., 2019; Elizabeth, 2010; Farina-Junior et al., 2017; Maia et al., 2019; Nornan et al., 2018; Sant'Ana et al., 2012; Sharp et al., 2014; Scotton et al., 2014, as cited in, Silva et al., 2021).

The gold standard treatment for venous leg ulcers is considered to be Compression therapy. (Alvarez et al., 2012; Falanga, 1996; Phillips et al., 1991; Moffat et al., 2003; Partsch, 2005, as cited in, Amsler et al., 2009). Single compression improvements have been made by using occlusive dressings to create an environment where fibrin is dissolved, enhancing epidermal migration, and increasing blood vessel growth. Most therapies for the treatment of CVU are directed on lowering venous hypertension, increasing wound cleansing, and enhancing tissue vascularization or oxygenation from the blood (Moffat et al., 2003, as cited in, Alvarez et al., 2012).

Non-adherent contact layer and compression treatment were used in the study of Alvarez et al. (2012) as the control group, where it was also mentioned that compression therapy with modified Unna's boot or a four-layer bandage system is accepted as standard care for the treatment of venous leg ulcers in the USA (Falanga, 1996; Phillips et al., 1991; Moffat et al., 2003, as cited in, Alvarez et al., 2012).

BC as wound dressings has been found to be sustainable, biocompatible, and biodegradable, with characteristics such as high surface area, flexibility, and capacity for chemical modification (Xianyu et al., 2014; Connor and Broome, 2018, as cited in, Zheng et al., 2020). BC's flexibility enables it to mold onto areas or wounds where it is applied (Cavalcanti et al., 2017; Ferreira et al., 2017; Lima et al., 2015; Martins et al., 2013; Pinto et al., 2016; Pita et al., 2015, as cited in, Silva et al., 2021; Vilar et al., 2016).

BC's high surface area can be attributed to its unique fiber network structure. This provides a large liquid loading capacity compared to plant-derived cellulose and cotton yarn (Meftahi et al., 2010, as cited in, Zheng et al., 2020). Subsequently, the fiber structure with a high aspect ratio and high surface area of BC leads to easier removal of the dressing (Chen et al., 2019, as cited in, Zheng et al., 2020). In addition, BC is characterized to have high tensile strength, permeable to gas and liquid, and has good compatibility with living tissue (Bielefeld et al., 2013; Sinno & Prakash, 2013; Das and Baker, 2016, as cited in, Zheng et al., 2020). It is also noted to not have any cytotoxic effects and adverse reactions to occur either short or long term when in contact with human skin (Zheng et al., 2020). Because of BC's chemical modification compatibility, it can be modified to meet the requirements of being an ideal wound dressing (Zheng et al., 2020).

Apart from BC as a promising wound dressing material, various modifications and developments were created to improve wound healing outcomes (Orlando et al., 2020; Zheng et al., 2020; Zmejkoski et al., 2018). BC is known for its outstanding properties such as low toxicity, thermal stability, biodegradability (Awadhiya et al., 2017), high tensile strength, and degradability (Portela et al., 2019). However, it lacks antimicrobial properties (Orlando et al., 2020; Sajjad et al., 2019; Savitskaya et al., 2019; Sulaeva et al., 2015; Zheng et al., 2020). For this reason, chronic wounds are highly prone to complications and may lead to excessive exudate production and inflammatory reaction due to the contamination of foreign bodies like bacteria (Lindsay et al., 2017; Wiegand et al., 2015). In addition, substantial loss of the skin's physical barrier also permits the entry of bacteria, thereby needing a new development of wound dressing that can promote healing and reduce bacterial infection (Rumbaugh et al., 2015; Zheng et al., 2020). The drawback is that BC synthesis is restricted to downward pellicle growth, which traps all microorganisms. There's also the drawback of BC culturing media, which is inefficient and costly (Kucińska-Lipka et al., 2015; Pinto et al., 2016).

Some studies have incorporated silver sulfadiazine (SSD) as an antimicrobial agent to compensate for the BC's lack of antimicrobial properties. SSD is an antimicrobial agent that can inhibit a broad spectrum of bacteria, including Staphylococcus aureus, Escherichia coli, and Pseudomonas aeruginosa, which are the chief causes of wound infection (Faisul Aris et al., 2019; Shao et al., 2015; Wen et al., 2015). Results have shown that the stability of BC impregnated with SSD is more remarkable than BC alone (Faisul Aris et al., 2019), and the impregnation of SSD exhibited suitable antibacterial activities and biocompatibility (Shao et al., 2015). Increasing the increment of SSD concentration incorporated into the BC also increases its tensile strength while directly reducing the BC membrane's porosity by filling up the porous matrix with SSD (Faisul Aris et al., 2019).

A study by Orlando et al. (2020) shows that chemical changes to functionalize BC could reduce bacterial growth by approximately one-half. Consequently, bio-cellulose adapted with blue nanosilver treatment is also effective in treating diabetic ulcers with good healing rate outcomes and minimal care requirements (Chansanti et al., 2020). Multiple studies have shown that bacterial cellulose successfully exhibited antibacterial properties and good biocompatibility with various modifications and wound dressing formulations (Faisul Aris et al., 2019; Chansati et al., 2020; Orlando et al., 2020).

2 RESULTS AND DISCUSSION

2.1 Mean Ulcer Area Reduction

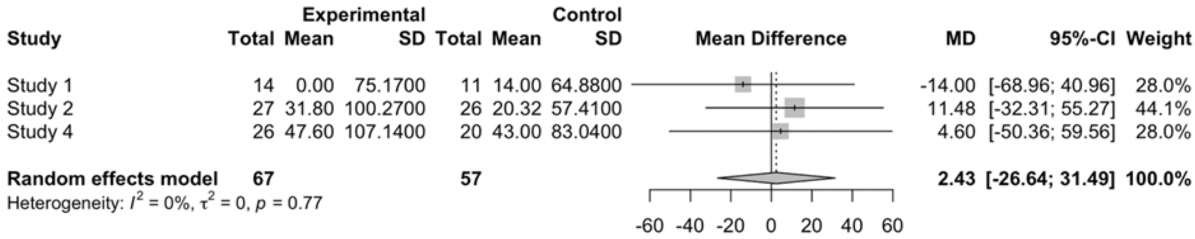

Figure 2. Forest Plot of the Meta-Analysis of the Effects of Bacterial Cellulose in Mean Ulcer Area Reduction

Combining the studies of Cavalcanti et al., Silva et al., and Dini et al., with 58 participants, the average ulcer area before and after treatment was 26.47 cm2 for the experimental group and 25.77 cm2 for the control group. This produced a 2.43 cm2 mean difference. The researchers are 95% confident that the average mean difference will fall between -26.64 and 31.49. The findings are statistically insignificant because the interval contains 0.

In terms of mean ulcer area reduction, the BC experimental group outperforms the conventional controlled group. This means that BC reduced the ulcer area after its application compared to the conventional treatment. Nonetheless, the results are said to be statistically insignificant because the confidence interval contains the null value (zero). Thus, there is no significant difference between both conventional and experimental treatments despite a "better" reduction seen in the experimental group. These findings coincide with the RCTs of Napavichayanun et al. (2018), Maurer et al. (2021), and Silveira et al. (2016). They deem no significant difference between BC and conventional treatments, despite having varied wound natures and definitions for conventional methods. These studies focused on split-thickness skin grafts, thermal injuries, and tympanic membrane perforations, yet all three note statistical insignificance between BC and conventional treatments in wound healing. Therefore, both methods are applicable for the reduction of mean ulcer area.

2.2 Pain Intensity

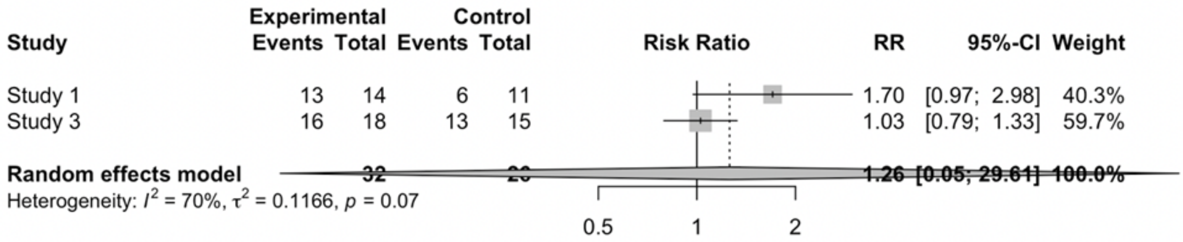

Figure 3. Forest Plot of the Meta-Analysis of the Effects of Bacterial Cellulose in Wound Pain Intensity

Combining Cavalcanti et al. and Alvarez et al., the prevalence of zero to mild pain in BC patients is 90.63%. Comparatively, 73.08% of respondents who received conventional treatment experienced mild pain. RR was 1.2583. This indicates a 25.83% increase in zero to mild pain prevalence when respondents receive BC treatment versus conventional treatment. The researchers are 95% confident that RR will be between 0.0535 and 29.6147. The findings are statistically insignificant since the confidence interval contains one (1).

Compared to the conventional treatment, the BC experimental group had a higher prevalence rate of zero to mild pain. Thus, individuals who received the BC treatment were more likely to experience less or no pain than those who received the conventional treatment. Similarly, lesser pain scores for the BC group are also noted in the clinical trials of Napavichayanun et al. (2018), Maurer et al. (2021), Silveira et al. (2016), and Oliveira et al. (2020), despite having different wound etiologies. However, there was no statistically significant difference between the two treatments, indicating that both can treat patients without inflicting excessive pain.

2.3 Appearance of Scar Formation

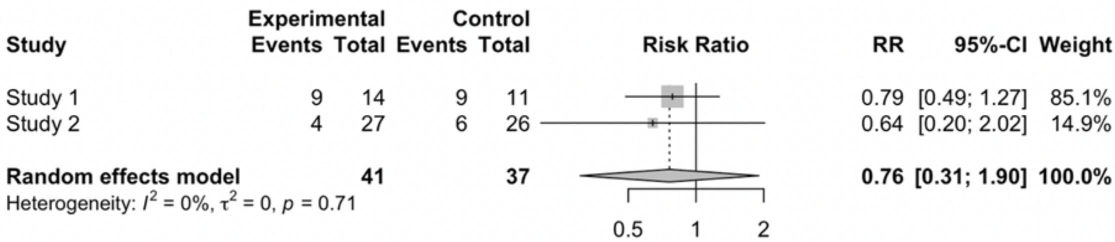

Figure 4. Forest Plot of the Meta-Analysis of the Effects of Bacterial Cellulose in Appearance of Scar Formation

Combining the studies of Cavalcanti et al. and Silva et al., the partial skin loss prevalence rate of respondents who received BC treatment is 31.71% and 40.54% for conventional treatment. RR = 0.7624. This indicates a 23.76% decrease in partial skin loss prevalence when using BC treatment versus conventional treatment. The researchers are 95% confident that RR will fall between 0.3054 and 1.9034. The findings are statistically insignificant since the confidence interval contains one (1).

Because a decrease is noted in the partial skin loss prevalence rate of the BC group compared to the conventional group, otherwise denoted as “a decrease in the absence of scar formation,” the conventional group seems to have a better result in this outcome. The results show that the conventional group is more likely to present with only partial skin loss or simply without scar formation. However, given that the findings are statistically insignificant, there is no difference between BC and conventional treatments in this outcome. Thus, both methods can lessen scar formation or skin loss after treatment.

2.4 Wound Healing Tissue

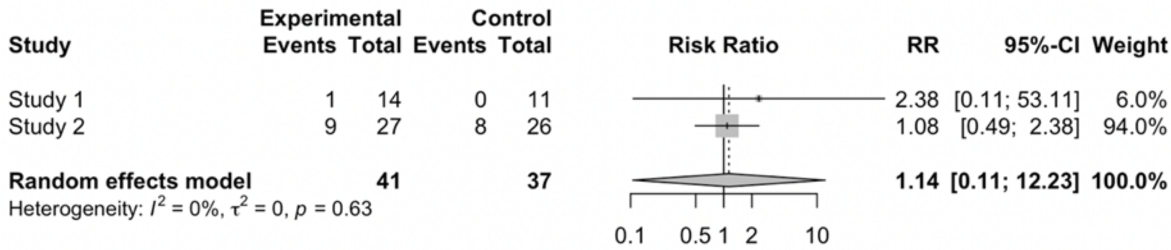

Figure 5. Forest Plot of the Meta-Analysis of the Effects of Bacterial Cellulose in Wound Healing Tissue

Combining the studies of Cavalcanti et al. and Silva et al., the wound healing prevalence rate of respondents who received BC treatment is 24.39% and 21.62% for conventional treatment. This resulted in an RR of 1.1358, which means that respondents receiving BC treatment had a 13.58% higher wound healing prevalence rate than those receiving conventional treatment. The researchers are 95% confident that RR will fall between 0.1055 and 12.2284. Despite these claims, the confidence interval contains the null value of one (1), meaning the findings are statistically insignificant.

Since the wound healing prevalence rate of the experimental BC group is increased compared to the conventional group, the BC group seems more likely to present with fully healed wounds than the conventional group. This means that the BC group is more likely to display completely healed and closed wounds. However, since the findings are also statistically insignificant, there is no difference between BC and conventional methods regarding wound healing tissue. Therefore, both methods may promote healthy tissue-type wounds after treatment.

Several studies have compared other wound treatment methods with bacterial cellulose-based wound dressings. Various authors used variables such as time to epithelialization, wound healing rate, pain intensity, presence of inflammation, scar appearance, and exudate quality to compare the outcomes. Napavichayanun and company's (2018) randomized clinical trial (RCT) compared the safety and efficacy of BC and commercial Bactigras® dressing in the treatment of split-thickness skin graft patients. The authors concluded that the formation of wound scars in the BC experimental group was of higher quality than the Bactigras® control group when comparing erythema and melanin values, Vancouver Scar Scale (VSS), and Transepidermal Water Loss (TEWL). Pain scores were also significantly lower in the experimental group. Maurer and company's (2021) RCT results coincide with those of Napavichayanun et al. (2018) since both studies' authors noted either lessened pain intensity or the absence of increased pain. Maurer et al. (2021) studied variables such as length of stay in the hospital, anesthesia procedures, and wound healing in pediatric victims of thermal injuries. Thirty-nine (39) patients received polyurethane foam as the control group, while 33 patients received bacterial nanocellulose as the experimental group. The authors concluded that bacterial nanocellulose offers more effectiveness in a pediatric population in terms of hospital stay and treatment with general anesthesia. It allows lessened hospitalization durations and faster surgeries under anesthesia. In addition to improvements in pain, scar quality, and hospital stay, Silveira et al. (2016) highlighted BC's superiority in cost-effectiveness and surgical time. The RCT by Silveira et al. (2016) was composed of tympanic membrane perforation patients. Twenty (20) patients received BC grafts, while the other 20 received autologous temporal fascia grafts. The experimental BC group took an average of 14.06 minutes to perform surgical procedures, while the fascia control group took 76.50 minutes. The fascia group's total hospital expenses cost approximately R$7,178.00 more than the BC group's total expenses. Factors that affected this decrease in costs could be the BC's features of lessened laboratory testing, needless general anesthesia and specialized surgical procedures, and shortened hospital stay.

However, while the studies mentioned above displayed improved conditions with BC in terms of pain, wound quality, hospitalization, and practicality, the wound healing rate or time to epithelialization was generally deemed statistically insignificant. Napavichayanun et al. (2018), Maurer et al. (2021), and Silveira et al. (2016) see no significant difference between wound healing, despite having different wound natures and definitions for conventional treatment. Colenci et al. (2019) seem to further reiterate this statistical insignificance in treating chronic venous ulcer patients. The RCT by Colenci et al. (2019) focused on comparing BC dressings and collagenase dressings, with its primary outcome centered on wound closure rate. While a more significant reduction in the wound size was apparent in the BC group, statistical analysis proved this insignificant.

The researchers of this study observed a pattern of statistical insignificance in the difference between the wound healing of the control and experimental groups, along with significant differences or improved conditions in other parameters such as pain, wound quality, hospitalization, and practicality. Despite the variety between these studies regarding wound nature, methodology, and conventional treatment, consistent findings are shared across all studies and authors. Thus, emphasis is put on the significance of this meta-analysis as it gathers relevant data on a defined group. It aims to find these behaviors of bacterial cellulose in previous literature and examine whether venous ulcer patients also experience similar effects when treated with BC. Once these observations are successful, the authors may recommend the clinical use of BC as an alternative for wound dressings.

3 METHODOLOGY

3.1 Study Design

This study is a meta-analysis done by systematically pooling results and data from existing studies. The data were treated with one statistical treatment to provide a conclusion with the highest level of evidence and greater statistical power.

Data collection was done by searching online databases for potentially related studies as primary data The keywords entered on the online databases were as follows: bacterial cellulose, wound dressing, chronic venous ulcer, and Randomized Controlled Trials. Inclusion and validation of the studies identified were done using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) model as (see Fig. 2), and the Risk of Bias 2 (RoB2) Assessment tool to counter-check for the validity and quality of the studies included.

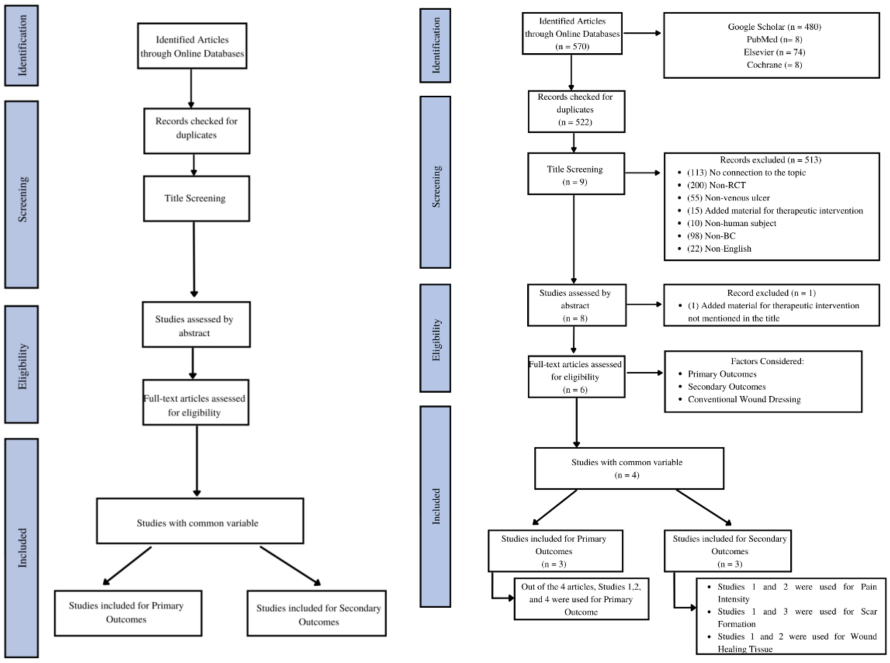

Figure 6. Flowchart showing the PRISMA Model. The PRISMA Model was used to verify inclusion into the meta-analysis

3.2 Selection Criteria

Table 1 shows the criteria that aided in the selection of the articles for this study. These were used to standardize the primary data and minimize variability in the included studies that ruled out possible extraneous factors that may skew the meta-analysis. Interventions in the randomized control trials that compared BC to conventional wound dressings were included in this study. It is important to note that some of these studies used commercially available cellulose. In contrast, others synthesized their BC membrane to impregnate certain chemicals that the retrospective authors deemed necessary. Investigations were limited to adults aged 40 - 95 years. In these studies, the retrospective authors explicitly excluded pediatric patients due to the unpredictability of the intervention outcome. Based on observation, there is variability in the kinds of wounds included in online and offline clinical trials. Because of this, inclusion criteria were narrowed to venous leg ulcers, whether of diabetic or non-diabetic etiology. The decision was made because most studies focused on this specific wound type in the treatment of BC. Studies with no primary outcome but with secondary outcome/s were still included to supplement information regarding the efficiency of the BC treatment

Table 1. Inclusion and Exclusion Criteria for the Selection of Articles.

	Inclusion Criteria	**Exclusion Criteria**
Bibliographic Databases	Elsevier (Elsevier, The Netherlands), PubMed (National Center for Biotechnology, Bethesda, Maryland, USA), Cochrane Library (Cochrane, London, United Kingdom), and Google Scholar (Google LLC, California, USA).	Databases outside these mentioned sites
Study Design	Randomized Controlled Trials	Meta-analyses similar to this study

Participants	Adult patients with chronic venous ulcers	Children or adolescents; Wounds caused by other diseases aside from chronic venous ulcers
Intervention	Bacterial Cellulose	-
Comparison	Bacterial Cellulose compared to a commercialized bandage	-
Outcome	Similar standard unit of measurements	-
Article Time Frame	No time constraint	-
Language	English	-

3.3 Data Extraction

Two independent reviewers (L.A.A & J.A.B) collected all published articles using a Google spreadsheet. The reviewers were assigned to extract data and mine relevant information about the studies, which were then entered into the spreadsheet. Information that was included were the title, author, email of the primary author, affiliated university, year published, database used, country of origin, language, study design, sample size, race/ethnicity, age group, gender, primary outcomes, secondary outcomes, and form of a conventional wound dressing. A third reviewer (C.A.C.P.) settled the conflict and reduced any possible bias in the extraction process in cases where there was disagreement on the data extraction process between the two independent review authors

3.4 Quality Assessment

Table 2. Summarized ROB-2 evaluations for each domain and overall evaluation.

	D1	**D2**	**D3**	**D4**	**D5**	**Overall**
Study 1: **Cavalcanti et al., 2017**	−	+	+	+	+	+
Study 2: **Silva et al., 2021**	+	+	+	+	+	+
Study 3: **Alvarez et al., 2012**	+	−	×	+	+	×
Study 4: **Dini et al., 2013**	+	+	×	+	+	×

Domains

D1: Bias due to randomization

D2: Bias due to deviations from intended intervention

+ Low

D3: Bias due to missing data
D4: Bias due to outcome measurement
D5: Bias due to selection of reported result

Some concern

High

In Table 4, the evaluators summarized the individual evaluations of each of the five studies included. While some studies were evaluated to have a high risk of bias, the authors opted to include the studies nonetheless into the meta-analysis to broaden the point of view from various perspectives.

The study conducted by Calvacani et al. (2017) was assessed and showed a low risk of bias. While the study had a low risk of bias in most domains, the main issues found by the evaluators include (1) lacking information with regards to the blinding and (2) the difference in the BMI of the control and experimental groups. As for the lacking information on the blinding to both participants and carers in the study, the authors were able to compensate by using standardized randomization procedure with software, strict adherence to procedure, consistent patient compliance, and meticulous measurements; blinding offers little to nonsubstantial risk for bias. The authors accounted for the issue of the possible interference on the BMI difference of participants by proper randomized allocation and assignments of intervention minimizing any risk of bias that may arise with regards to the confounding factor. The methodology utilized by the authors was also sound and based on existing validated frameworks. As guided by principles of the assessment tool, despite having the latter issues discussed, the study showed little to no bias as per other factors such as measurements, compliance, and monitoring was accurate and precise, showing pure objectivity of the study.
Similarly, the study conducted by Silva et al. (2021) also showed a minimal to low risk of bias. Following the risk assessment tool, the only issue that the evaluators have pointed out was the (1) lack of blinding to both the participants and the assigned carers administering the interventions and (2) differences in the frequency of the changing of the dressings. The lack of blinding shows little to no bias, given that the measurements were done through imaging software following the strict adherence to the purely objective framework. The authors counteracted any potential biases that may arise due to the differences in the frequency of bandage change by using a standardized measurement tool that was used across all groups. Subsequently, the study may have included a potential source of interference and bias through the participants' usage of several medications for the confounding comorbidities such as silver sulfadiazine, yet the yielded data has shown that these medications showed no significance ($p>0.05$), confirming that this factor was not an issue nor may be a potential contributor for any biases. Despite the problems discussed, the study showed minimal to no bias.

Contrary to the previous studies, the study of Alvarez et al. (2012) was evaluated to be of high risk of bias due to having a domain with "some concerns" and another with "high risk." Specifically, these domains were due to deviations from the intended interventions (Domain 2) and missing outcomes data (Domain 3), respectively. The randomization process of the study has a low risk of bias since the allocation sequence for bio-cellulose dressing (BWD), and the control group was based on the block randomization schedule. The randomization was done using sealed envelopes. However, the participants in the study are possibly aware of the allocated treatment regimen since sealed envelopes were opened after confirming that these patients are eligible for inclusion in the trial. Subsequently, in domain 3, a high risk arose from the missing outcome data caused by the high percentage of withdrawn patients in the control group with 35% (n=8) and the BWD-treated group with 28% (n=7). Although most withdrawals for both groups were due to non-concordance and protocol violations (n=3 BWD, n=4 control), there are still several withdrawals due to loss of follow up (n=3 BWD, n=2 controls) and infection (n=2 controls) that is beyond the scope to be evaluated but deemed to be possibly not related to the treatment given.

The following study, Dini et al. (2013), was also evaluated to have a high risk of bias due to the missing outcomes data domain. The study was unable to meet the minimum required of patients (n=50) to obtain a statistically significant difference due to 4 patients who could not complete the study because of protocol violations. On the other hand, the randomization process domain was assessed to have a low risk of bias since the allocation sequence was based on a computer-generated randomization schedule. No information was provided for deviations from the intended intervention domain if the patient's assigned intervention remained concealed during the trial. However, this was overruled by other signaling factors since the evaluation of the treatment was performed blinded, and non-protocol interventions were balanced across groups. Similarly, the measurement of the outcome domain and selection of the reported result domain was evaluated to have a low risk of bias. Parametric or nonparametric statistical analyses were appropriately performed using the Mann-Whitney U test, 2-way analysis of variance, and W2 test. At the same time, Statistical Package for Social Sciences (SPSS version 16.0) was performed for the intention-to-treat analysis. Although the risk of bias may be pertinent due to the exclusion of 4 patients, the study was able to show a trend using objective parameters (TEWL, Chroma Meter, Corneometer) that consistently aligned with one another. Lastly, the result reflects the multiple initial measurements without omitting a particular calculation that may lead in the direction of favoring a specific outcome measurement.

Journal articles were assessed further using the RoB-2 software. This tool validated the relevance and applicability of the journal articles selected using the inclusion and exclusion criteria. The authors aligned the basis of judgment with RoB-2's signaling questions matched with the study's research design. Three authors were assigned to validate the quality using RoB-2. Validation was done mainly by S.J.P. and T.Y.L., while a third reviewer, J.C.C., resolved conflicts between the two.

4 CONCLUSION

Despite the results being in favor of the BC group in terms of pain intensity and wound healing tissue, this meta-analysis found no significant evidence that bacterial cellulose as a wound dressing has efficiently improved wound management among adult patients with venous ulcers. Specifically, BC did not significantly demonstrate a better result in mean ulcer area reduction, pain intensity, scar formation, and wound healing tissue than conventional methods. Therefore, the authors suggest that one may use either the BC or the conventional methods as these do not significantly differ. Furthermore, it is essential to note that this analysis has only included four RCTs, two of which are deemed to be of considerable risk of bias, which may affect the reliability and accuracy of the results. Given that the scarcity of RCTs included may negatively affect the results, the authors recommend that more RCTs of the same subject matter be conducted so more data can be analyzed. Moreover, since the authors supposedly conclude no significant difference in mean ulcer area reduction, pain intensity, and wound healing tissue, other parameters may be explored. Thus, future systematic reviews and meta-analyses can further compare BC and conventional treatment methods in terms of infection rate, allergy prevalence, exudate quality and quantity, wound edge type, cost and production, availability of materials, convenience or ease of dressing change, and sustainability. Furthermore, BC may be applied to other wound types, such as burns, skin grafts, and ischemic wounds.

ACKNOWLEDGEMENTS: The researchers would like to extend their warmest and deepest gratitude to the following for their instruction and unwavering support towards the completion of this research proposal:

First and foremost, the Almighty God, for providing the researchers with strength, inspiration, and guidance. It is through Him that this research is possible.

The University of Santo Tomas Faculty of Pharmacy, for the institution's support in this endeavor.

Ms. Sherill D. Tesalona, RMT, MSMT, for her patience, guidance, and encouragement throughout the whole process of this research. Her steadfast belief in the researchers' capabilities is a massive factor in the pursuance of this undertaking.

Dr. Ronald P. Cabral, for offering his invaluable expertise as a collaborator. His vision for this study as a potentially helpful tool in the practice of evidence-based medicine deeply inspired the researchers to push through with this topic.

Ms. Debra Hope Timog, their statistician, for her guidance and wisdom, as well as the time she has generously provided for the researchers. Her understanding of study design and statistical tools was very helpful as she was able to guide the researchers by giving the authors knowledge on how to better improve the research.

Friends and family, for their support, prayers, and sacrifices for educating and preparing the researchers for their futures and for continuing this research.

The researchers are very thankful for all these people. Without them, continuing this research would have been a lot more difficult, if not impossible.

FUNDING: The partnership between the two parties under this MOA will not involve financial commitments of any kind. It was agreed upon by both parties during the first meeting that the Collaborator shall contribute in exchange of acknowledgement in the writing of the thesis paper. Apart from such fulfillment, there will be no transfer of funds between the researchers and the Collaborator. This research received no external funding.

CONFLICT OF INTEREST: Authors declare no conflict of interest.

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